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Cisplatin and Etoposide Versus Cyclophosphamide, Epirubicin and Vincristine in Small Cell Lung Cancer: a Randomised Study

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From September 1986 until December 1991, 139 patients with histologically-proven small cell lung cancer, age < 75 years, performance status > 40, absence of brain metastases and no previous treatment, were randomised to receive either CEV cyclophosphamide 1000 mg/m² intravenous (i.v.), epirubicin 70 mg/m² i.v., vincristine 1.2 mg/m² i.v., every 3 weeks or PE (cisplatin 20 mg/m² i.v. and etoposide 75 mg/m² i.v. for 5 consecutive days, every 3 weeks) for six cycles. After three cycles, responding patients received radiotherapy to the chest (45 Gy/15 sessions) and to the brain (30 Gy/10 sessions—only in patients with limited disease achieving complete remission). 3 patients were ineligible. Patient characteristics included (CEV/PE) total number 66/70, median age 60/61 years, median performance status 80/80, extended disease 33/48 cases ($P = 0.04$). In evaluable patients, 42/62 (67.7%) responded to CEV while 42/58 (72.4%) responded to PE (P = non-significant); respective complete response rates were 16.1 and 29.3% (P = non-significant) and respective complete response rates in patients with extended disease were 9.4 and 28.9% ($P = 0.03$). Median survival was 10.5 months, without significant differences in the two treatment arms, even after adjustment for stage. PE was less well tolerated than CEV. Although PE is more active than CEV in certain subsets of patients, its apparent inability to improve survival in this and in other studies questions its routine use in small cell lung cancer.

Key words: small cell lung cancer, chemotherapy
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INTRODUCTION

CHEMOTHERAPY IS the mainstay of treatment of small cell lung carcinoma (SCLC), and response rates in the order of 60–90% with a 20–50% complete response rate are achieved by various chemotherapeutic regimens [1]. The combination of cyclophosphamide, doxorubicin and vincristine (CAV) was identified in the late 1970s as a relatively safe and effective treatment [1], and is also largely used because of its convenience and ease of administration. In more recent years, the combination of cisplatin and etoposide (PE) has been found to be active both as second-line [2, 3] and as induction treatment [4, 5]. In particular, a 5-day schedule of the PE combination yielded, in our hands [5], a 90% response rate (31% complete response rate) with a median survival of 15 months in limited disease (LD) and of 9.3 months in extended disease (ED). Particular interest was raised by the concept of alternating the two regimens which were supposed to be, at least partially, non cross-resistant. Alternating CAV and PE have been compared in randomised studies to CAV, and an

improved median survival time in ED was reported in one study [6]; however, it was not clear whether this was due to the early exposure of the tumour to several active drugs or, more simply, to the superiority of PE over CAV.

In patients with LD, radiation therapy to the chest can reduce the rate of local relapse with survival advantage, as shown by a recent meta-analysis of published randomised studies [7]. Prophylactic cranial irradiation (PCI) in patients responding to chemotherapy can reduce the frequency of cerebral metastases, although the final impact upon survival remains uncertain [8].

In 1986, since a randomised comparison of CAV and PE had, at that time, not been reported, we started a study in which patients with SCLC, LD or ED were randomised to one of two treatment arms involving six cycles of chemotherapy plus radiation therapy, differing only in the type of chemotherapy involved (CAV versus PE). In the CAV arm, doxorubicin was substituted by epirubicin (CEV regimen), an anthracycline derivative with superimposable activity [9] and less cardiotoxicity [10], with a 55% dosage increase as compared to the doxorubicin dosage in a current CAV regimen [11]. The PE schedule adopted was the same previously evaluated by us [5].

The results of that study are the subject of the present report.

PATIENTS AND METHODS

From September 1986 until December 1991, 139 consecutive patients seen at our institutions were enrolled into the study. None of the cooperating institutions randomised patients through the entire 63-month period. The total number of months-Institution amounted to 126, for an average accrual of 1.1 patients/month per institution. Conditions of eligibility included: histological proof of SCLC, age < 75 years, Karnofsky performance status (PS) > 40, serum creatinine values within normal limits, adequate liver (serum bilirubin < 2 mg/dl) and cardiac functions, absence of brain metastases and no previous treatment. Staging procedures included clinical examination, chest X-rays, bronchoscopy, cerebral scintigram or CT scan, bone scan, liver echography, scintigram or CT scan, bone marrow aspirate and biopsy (only in patients with apparently limited disease), peripheral blood cell counts, determination of serum glucose, urea, electrolytes, creatinine and liver function tests. Disease stage was classified as LD, defined as tumour involvement confined to one hemithorax, including ipsilateral supraclavicular nodes, or ED, with tumour beyond these sites; patients with malignant pleural effusion were considered to have ED.

After stratification per institution, patients were randomised to receive either CEV [cyclophosphamide 1000 mg/m^2 intravenous (i.v.), epirubicin 70 mg/m^2 i.v., vincristine 1.2 mg/m^2 i.v., every 3 weeks - the dose of vincristine was not to exceed 2 mg] or PE (cisplatin 20 mg/m^2 i.v. for 5 consecutive days and etoposide 75 mg/m^2 given as a 45-min i.v. infusion on the same days, plus 1000 ml of i.v. fluids with 100 g of mannitol daily).

Peripheral blood cell counts and renal function tests were carried out before each course of treatment; after three cycles, bronchoscopy and all initially positive examinations were repeated.

At that point, responding patients received radiation therapy (45 Gy in 15 sessions), which was delivered to the chest in cases presenting with LD, while patients with ED also received radiation to massive, critical areas of extrathoracic spread. Patients with LD achieving complete remission (CR) also received prophylactic brain irradiation (30 Gy in 10 sessions, concomitantly with chest irradiation).

After radiation, three additional cycles of chemotherapy were administered with attenuated dosage (in the CEV regimen cyclophosphamide 700 mg/m^2, in the PE regimen etoposide 50 mg/m^2).

At the end of treatment, response was reassessed by repeat examination of all disease parameters. No further treatment was given to patients in clinical CR at the end of treatment, even if microscopic residual disease was noted (failure to obtain pathological CR). Patients resistant to chemotherapy or relapsing within 6 months from the end of treatment were crossed over to the alternative regimen, while those patients relapsing later than 6 months were rechallenged with the induction regimen.

Tumour response and toxicity were defined according to standard WHO criteria [12]. Response was categorised as CR, partial remission (PR), stable disease and progression. The χ^2 test [13] was used to evaluate the differences between proportions. Survival time was calculated from the day treatment was started. Survival curves were plotted according to the Kaplan–Meier product limit method [14]. Multivariate analysis was based upon the Cox proportional hazard regression model [15].

116 evaluable randomised patients were anticipated in order to detect a 20% difference (CEV = 70%, PE = 90%) in response rate (α = 0.05, power = 0.80).

RESULTS

A total of 139 patients were enrolled in the study. Three patients were retrospectively found to be ineligible (brain metastases in 2 patients, non-small cell histology in 1 patient). The main characteristics of the 136 eligible patients are reported in Table 1. A statistically significant prevalence of patients with ED in the PE arm occurred by chance.

16 patients (4 CEV and 12 PE) were not evaluable for response because they never started treatment (1 CEV, 3 PE), were lost to follow-up (1 CEV, 8 PE), developed non-neoplastic disease

Table 1. Patients' characteristics

	CEV	PE
Total number	66	70
Male/female ratio	59/7	60/10
Median PS (range)	80(50/100)	80(50–100)
Median age (range)	60(41/70)	61(41/70)
LD/ED	33/33*	22/48*

*P = 0.04.

CEV, cyclophosphamide, epirubicin, vincristine; PE, cisplatin, etoposide; PS, performance status; LD, limited disease; ED, extended disease.

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This study was carried out within the framework of the North-Eastern Italian Oncology Group (G.O.C.C.N.E).
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Table 2. Response

	CEV	PE	
Total number	66	70	
Not evaluable	4	12	
Evaluable	62	58	
Complete response	10	17	
Partial response	32	25	
Stable disease	8	9	
Progression	12	7	
Response rate	67.7% (42/62)	72.4% (42/58)	$P = 0.72$
Complete response rate	16.1% (10/62)	29.3% (17/58)	$P = 0.13$

precluding evaluation (1 CEV) or died early because of toxicity (1 CEV, 1 PE).

Of the 120 evaluable patients (62 CEV, 58 PE), 67 (35 CEV, 32 PE) were able to complete the planned treatment. Reasons for discontinuation included absence of response (20 CEV, 16 PE) and non-compliance to treatment (7 CEV, 10 PE). All responding patients received chest irradiation. 10 additional CEV and 3 additional PE patients received radiation therapy because of symptoms. Only 6 patients (3 CEV, 3 PE) of the 11 presenting CR after the three induction cycles received PCI.

The responses obtained are reported in Table 2. The complete response rate was higher in PE patients, but not to a statistically significant extent. In the 55 patients with LD (50 evaluable), CEV yielded a 70% (21/30) response rate and a 23.3% (7/30) CR rate, PE an 80% (16/20) response rate and a 30% (6/20) CR rate. In the 81 patients with ED (70 evaluable), response rate and CR rate to CEV were 65.6% (21/32) and 9.4% (3/32), respectively, while a 68.4% (26/38) response rate and a 28.9% (11/38) CR rate were obtained with PE. The higher CR rate induced by PE in ED patients attained statistical significance ($P = 0.03$), while

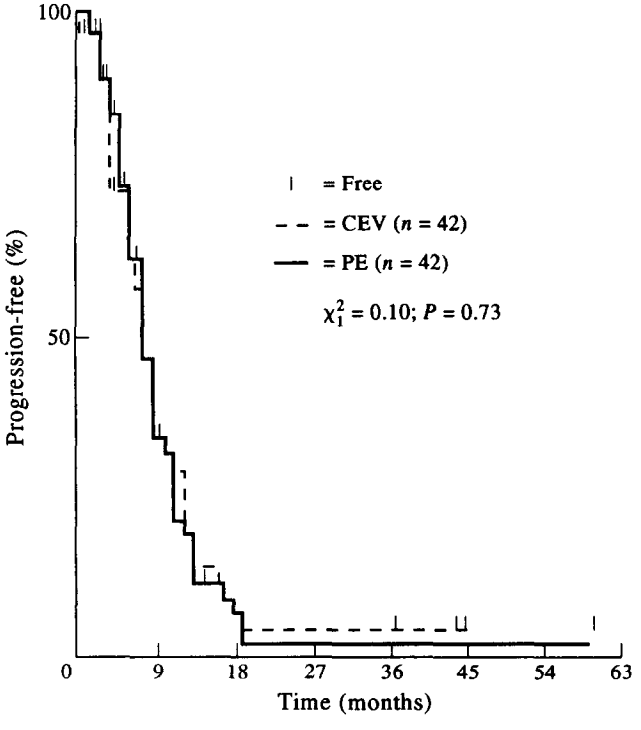

Figure 1. Duration of response.

Table 3. Sites of initial relapse

	CEV	PE
Not evaluable	12	10
Chest	10	14
Brain	10	11
Lymph nodes	1	3
Bone	5	2
Abdomen	3	2
Skin	1	-

none of the other differences in activity of the two regimens was statistically significant.

At evaluation after the three induction cycles, the response rate was 53.3% (33/62) for CEV and 51/7% (30/58) for PE. In 9 CEV patients and in 12 PE patients, radiotherapy and three additional chemotherapy cycles improved response.

Duration of responses in the two treatment arms is shown in Figure 1. The median duration of response was 8.1 months, without statistically significant differences between the two treatment arms.

Sites of initial relapse are shown in Table 3. Brain metastases as initial sign of progression occurred in 21 patients (10 CEV, 11 PE); none of those patients had received PCI.

Crossover salvage chemotherapy was employed in 52 cases (CEV in 13 patients, PE in 29); 3 of the 11 evaluable cases treated with salvage CEV had a PR, while PE induced a response in 15/28 evaluable CEV-resistant patients, with one CR.

The toxic effects encountered in the two treatment arms are reported in Table 4. Overall, toxicity was acceptable with both regimens, but PE was less well tolerated, with a greater ($P = 0.02$) incidence of grade 3–4 nausea and vomiting. Bone marrow toxicity was more frequent with PE, but not to a statistically significant extent. Two toxic deaths occurred (1 CEV, 1 PE), related to infectious complications during leucopenia.

Overall median survival (all eligible patients) was 10.5 months (LD = 12.7 months, ED = 9 months). The survival curves of patients treated with CEV and with PE are reported in Figure 2, showing no statistically significant survival differences even after adjustment for stage. The median survival of patients treated with CEV and PE was 10.7 and 9.8 months, respectively. Two-

Table 4. Toxicity

	CEV (56 evaluable patients)				PE (56 evaluable patients)			
	G1	G2	G3	G4	G1	G2	G3	G4
Nausea and vomiting	13	12	6	0	10	14	13	3
Mucositis	8	11	10	0	13	9	6	1
Diarrhoea	0	0	0	0	1	1	0	0
Cardiotoxicity	2	0	0	0	1	0	0	0
Renal toxicity	1	0	0	0	2	0	0	1
Neurotoxicity	11	3	1	0	8	7	0	0
Leucocytes	13	13	6	1	8	17	8	2
Platelets	1	4	0	0	3	5	2	1
Haemoglobin	4	3	1	0	2	6	2	1
No toxicity	5				4			

Table 5. Three studies compared

	Roth [18] CAV	PE	Fukuoka [19] CAV	PE	Present study CEV	PE
No. evaluable patients	140	140	95	95	62	58
% extended disease	100	100	48	54	50	69
Response rate (%)	51	61	55	78	68	72
Complete response (%)	7	10	15	14	16	29
Median response duration (months)	4.0	4.3	6.2	6.4	8.2	7.8
Median survival (months)	8.3	8.6	9.9	9.9	10.7	9.8

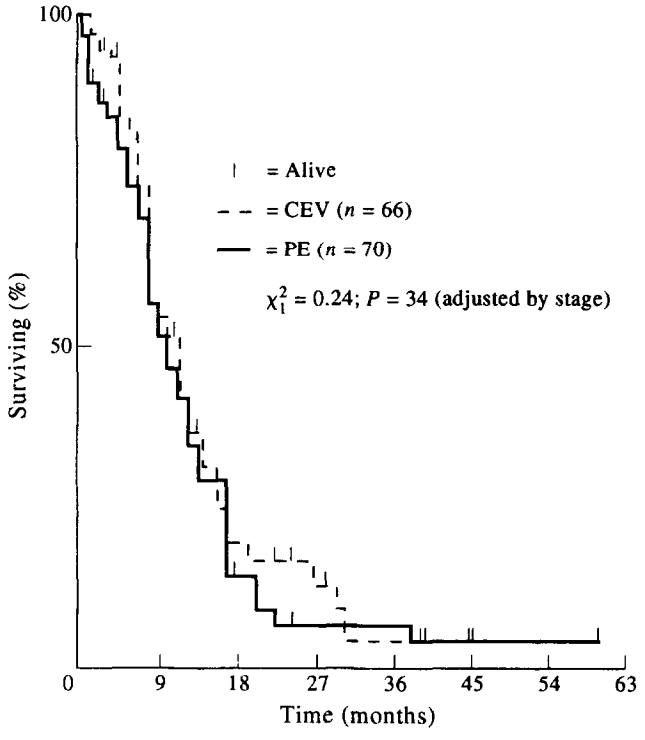

Figure 2. Overall survival.

year survival was 8% for CEV and 16% for PE. Even when LD and ED patients were considered separately, no survival differences between the two treatment arms emerged.

DISCUSSION

The initial enthusiasm for chemotherapy in SCLC, reinforced by the observation of a proportion of patients apparently cured from the disease, has partly been tempered by the apparent lack of subsequent improvement, particularly in terms of survival.

In this study, the overall survival of LD and ED patients was 12.7 and 9 months, respectively, with no significant differences between the two treatment arms. CR rate was 22.5% overall, with a slight superiority for PE. These results, obtained in a cooperative setting, appear to be worse than those observed in our previous monoinstitutional experience with PE [5]. It is likely that the present results reflect the situation 'on the field' better than the monoinstitutional studies. In effect, a large survey on the long-term results of protocol and non-protocol patients at numerous Italian institutions [16] demonstrated a low incidence of long-term survivors (6.1% disease-free survival at 2 years), confirming that results obtained in pilot studies may be difficult to reproduce in a wider setting.

In this randomised study, the activity of PE and CEV appeared to be overall superimposable in terms of response rate (72.4% for PE and 67.7% for CEV), with a tendency to a higher incidence of CRs in PE patients, and a statistically significant higher CR rate in ED patients treated with PE. Duration of response and overall survival were superimposable. The pattern of relapse was also similar. In particular, an equal incidence of brain metastases as first sign of progression was noted in CEV- and PE-treated patients, which was disappointing taking into account the activity of etoposide against overt brain metastases from small cell lung carcinoma [17]. Toxicity differed somewhat in the two treatment arms. Although both treatments were generally devoid of prohibitive toxicity, PE was overall less well received, because of a higher incidence of nausea and vomiting (the new serotonin antagonists were not used in this study) and bone marrow toxicity. Moreover, its 5-day schedule made it less convenient to the patients than CEV.

Two randomised studies [18, 19] have addressed the issue of the relative merits of CAV and PE. Their main results, together with the results of the present study, are summarised in Table 5. In all three studies, there is a tendency to some superiority of PE in terms of response rate or CR rate, while duration of response and survival appear to be superimposable. In the two aforementioned studies, a third arm (alternating chemotherapy) was present. While alternating chemotherapy was modestly more effective than single regimens in the Japanese study (particularly in LD patients) [19], in the American study [18] no superiority of alternating chemotherapy was detected. These findings, together with those of the Canadian study [6], showing the superiority of alternating CAV/PE over CAV, appear to support the concept of some superiority of PE over CAV or CEV, and of a consequent therapeutic advantage (not observed in all studies) of alternating chemotherapy over CAV. A pooled analysis of published studies might be warranted to answer the question.

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Metastatic Medulloblastoma: the Experience of the French Cooperative M7 Group

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A retrospective analysis was performed to determine the outcome of children with metastatic medulloblastoma given a standardised treatment programme. Of 68 consecutive patients treated in the French M7 protocol for medulloblastoma, 23 presented with metastatic disease. They were uniformly treated with surgery, and the same protocol of chemotherapy and craniospinal radiotherapy. The 7-year relapse-free survival rate is 43% for metastatic patients compared to 68% for patients with localised disease. Survival did not correlate with age, sex, location of metastases, extent of initial surgery and the dose of radiation therapy on the posterior fossa. Survival did correlate with the dose to the cranial field with a threshold dose of 30 Gy. Patients with metastatic disease have a worse prognosis and require more aggressive therapies at initial presentation. The prognostic impact of the different sites of metastatic disease requires further evaluation in cooperative studies.

Key words: medulloblastoma, metastatic disease, chemotherapy, radiotherapy, prognostic factors
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INTRODUCTION

DUE TO major advances in surgery, chemotherapy and radiotherapy, the prognosis of medulloblastoma has dramatically improved in the last 20 years. Recent series report an overall disease-free survival at 10 years of 50–60% [1–3]. However, if metastases are present at diagnosis, the survival rate is obviously worse, ranging from 30 to 40% [4]. Moreover, the survival difference between patients with localised and metastatic disease may actually be even greater, since many patients classified as having no metastasis (Mo) had neither cerebrospinal fluid (CSF) cytology examination nor a myelogram at diagnosis. The optimal management for patients with metastatic medulloblastoma at